



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Herndon

FILED: July 9, 2001

SERIAL NO.: 09/901,429

FOR: β -Adrenergic Blockade Reversal
Of Catabolism After Severe Burn

§ ART UNIT: 16

§ EXAMINER:
§ Kim, Vickie

§ DOCKET: D641

TECH CENTER 1600/2900

JAN 24 2003

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Assistant Commissioner of Patents
Washington DC 20231

TRANSMITTAL OF APPEAL BRIEF

Dear Sir:

Enclosed please find three originals of the Appeal Brief for the above-referenced patent application.

The Commissioner is hereby authorized to charge Deposit Account No. 07-1185 in the total amount of \$160 for the appeal fee and any additional fee that may be required. Please credit any overpayment or debit any underpayment to Deposit Account 07-1185.

Date: Jan 15, 2003
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Respectfully submitted,

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Dear Sir:

I hereby certify under 37 CFR 1.8 that the following correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to Box AF, Assistant Commissioner of Patents, Washington DC 20231:

- (1) Transmittal of Appeal Brief; and
- (2) Three (3) copies of Appeal Brief.

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Respectfully submitted,

Benjamin Aaron Adler
Benjamin Aaron Adler, Ph. D., J.D.

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TECH CENTER 1600/2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Herndon

FILED: July 9, 2001

SERIAL NO.: 09/901,429

FOR: β -Adrenergic Blockade Reversal
Of Catabolism After Severe Burn

§ ART UNIT: 1600/2000
§
§ EXAMINER:
§ Kim, Vickie
§
§
§ DOCKET: D6414
§

Assistant Commissioner of Patents
Washington, D.C. 20231

ATTENTION: Board of Patent Appeals and Interferences

APPELLANT'S BRIEF

This Brief is in furtherance of the Notice of Appeal filed in this case on December 11, 2002. In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate. The fees required under 37 C.F.R. §1.17(c) and any other required fees are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

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INDEX OF SUBJECT MATTER

	<u>Page</u>
5	
I. Real party in interest	3
II. Related Appeals and Interferences	3
10 III. Status of Claims	3
IV. Status of Amendments	4
V. Summary of Invention	4
15	
VI. Issues	5
VII. Grouping of Claims	6
20 VIII. Arguments	6
IX. Appendix	
A. CLAIMS ON APPEAL	14
B. Cited Reference	

I. REAL PARTY IN INTEREST

The real party in interest is Research Development Foundation, the Assignee, as evidenced by an Assignment recorded in the Patent and Trademark Office at Reel 012938, Frame 0584 on May 28, 2002.

II. RELATED APPEALS AND INTERFERENCES

Appellant is aware of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

Originally claims 1-20 were filed with this Application. Claims 14-20 were withdrawn from further consideration by the Examiner as being drawn to non-elected inventions. Claims 8 and 13 were canceled. The pending claims 1-7 and 9-12 are being appealed of which claims 1 and 9 are independent claim.

IV. STATUS OF AMENDMENTS

Claims 1, 7 and 9 have been amended. No amendment was made in response to the Final Office Action mailed October 8, 2002.

5 All pending claims are shown in Appendix A.

V. SUMMARY OF THE INVENTION

The present invention demonstrates that blockade of β -
10 adrenergic stimulation with orally administered propranolol decreases
resting energy expenditure and net muscle catabolism (page 3, line 12
to page 4, line 17; page 23, lines 10-14; Figure 2). Twenty-five acute,
severely burned (>40% total body surface area) children were studied
in a prospective, randomized trial. Thirteen of the subjects received
15 oral propranolol for at least two weeks, and twelve served as non-
treated controls. During beta blockade, heart rates and resting energy
expenditures of the propranolol group were lower than baseline and
lower than those of the control group ($p < 0.05$). Corresponding to the
significant differences in heart rate and resting energy expenditure,
20 muscle protein net balance improved 82% relative to pre-treated
baseline in the subjects treated with propranolol while it decreased

27% in the non-treated control subjects ($p < 0.05$). These data indicate that propranolol attenuates hypermetabolism and reverses muscle protein catabolism in burn victims when administered for an extended period during acute hospitalization.

5

Thus, the present invention is drawn to a method of treating an individual having a severe burn by administering to the individual a pharmacologically effective dose of a beta-adrenergic antagonist, wherein treatment with the beta-adrenergic antagonist improves skeletal muscle protein kinetics in the individual as compared to individual without the treatment. In one embodiment, the beta-adrenergic antagonist is propranolol.

15

VI. ISSUES

35 U.S.C. §102(b)

Whether claims 1-7 and 9-12 are anticipated under 35 U.S.C. §102(b) by Herndon et al.

20

VII. GROUPING OF CLAIMS

The rejected claims stand or fall together.

5

VIII. ARGUMENTS

The Rejection Under 35 U.S.C. §102

In the Final Office Action mailed October 8, 2002, claims 1 - 7 and 9-12 were rejected under 35 U.S.C. §102(b) as being anticipated by Herndon et al. The rejection is respectfully traversed.

10

Claims 1 and 9 are drawn to methods of treating an individual having a severe burn, wherein said treatment with beta-adrenergic antagonist or propranolol improves skeletal muscle protein kinetics in said individual as compared to individual without the treatment (page 4, lines 8-12). In contrast, Herndon et al. taught that treatment with beta-adrenergic antagonist such as propranolol had no effect on protein metabolism in burn patients (see page 1301, Results section; page 1304, left column, second and third paragraphs). Herndon et al. did not teach or suggest treatment with beta-

adrenergic antagonist or propranolol would improve skeletal muscle protein kinetics in burn patients as claimed herein.

Applicant submits that the Examiner erred in asserting
5 that "the cited reference meets all the critical elements required by the claims. Thus, all the claimed subject matter is anticipated by the cited reference" (Final Office Action, page 3). The methods claimed by the Applicant relate specifically to improved skeletal muscle protein kinetics in burn patients. In contrast, the cited Herndon et al.
10 reference taught a method that had no effect on protein metabolism. Herndon et al. disclosed that "the rate of appearance of leucine, used as an index of total body protein catabolism, was not significantly altered by either β -blocker" (page 1301, last sentence of Results). Therefore, Herndon et al. taught a method that had no effect on
15 protein metabolism. Herndon et al. clearly did not teach or suggest a method that would improve skeletal muscle protein kinetics as claimed herein.

The Examiner contended that "skeletal muscle kinetic
20 improvement is naturally occurring when β adrenergic antagonists are administered to the patient with burns, and thus it is considered to be inherent feature" (Final Office Action, page 3, point 3). Applicant

submits that the Examiner's conclusion is without basis and directly contradicts with the teaching in Herndon et al. Herndon et al. concluded their study by stating that:

5 In the present study, we failed to document an effect of
propranolol and metoprolol on protein kinetics, although
an earlier study indicted an increase in urea production
with propranolol. That study used four patients who
were aged 2 to 4 years, and the response in young
10 children may differ from that in older children. It is also
possible that the level of stress was higher. Finally, the
short-term changes in urea production may not always
correspond to changes in net protein breakdown. For this
reason, in the present study, we used two independent
15 approaches of assessing net protein breakdown. The fact
that neither of these techniques revealed any significant
effect of either agent on protein kinetics indicates that
the effect is of minimal clinical concern.

20 In summary, selective β 1-adrenergic and nonselective
adrenergic receptor blocking agents can significantly
reduce heart rate and myocardial oxygen consumption in
hypermetabolic burned patients without adversely
affecting protein kinetics. (page 1304, left column, second
and third paragraphs)

Hence, Herndon et al. clearly taught that treatment with β -adrenergic antagonists or propranolol had no effect on protein kinetics in the treated individuals. Herndon et al. did not teach or suggest treatment with β -adrenergic antagonists had an inherent feature of improving skeletal muscle protein kinetics. Furthermore, the Examiner's assertion that skeletal muscle protein kinetic improvement is an inherent feature of treatment with β adrenergic antagonists is not consistent with the teaching of Herndon et al.

The Examiner has not provided any scientific reference or experimental data that would allow one of ordinary skill in the art to conclude that skeletal muscle protein kinetic improvement is an inherent feature of treatment with β adrenergic antagonists. Applicant submits that in the absent of the data disclosed herein, one of ordinary skill in the art would have no basis to conclude that treatment with β adrenergic antagonists would improve skeletal muscle protein kinetic. Therefore, the Examiner has fallen victim to the insidious effect of hindsight syndrome wherein that which was taught in the invention by the Applicant is being used against its inventor.

In the Advisory Action mailed November 20, 2002, the Examiner contended that "improving muscle protein metabolism is inherently possessed feature whether the said pathway has been known (discovered) in the art or not." Applicant respectfully
5 disagrees.

First of all, Herndon et al. clearly taught that treatment with β adrenergic antagonists or propranolol had no effect on protein kinetics. Herndon et al. did not teach or suggest treatment with β
10 adrenergic antagonists would improve skeletal muscle protein kinetics as claimed herein. Therefore, in view of Herndon et al., one of ordinary skill in the art would have no reason to believe or suspect improving muscle protein metabolism is an inherent feature of treatment with β adrenergic antagonists. Neither did the Examiner
15 provide any evidence that would support the inference that improving muscle protein metabolism is an inherent feature of treatment with β adrenergic antagonists.

Moreover, Applicant submits that instead of disclosing an
20 inherent feature of treatment with β adrenergic antagonists, the present invention provides results that are unexpected in view of the

prior art. Herndon et al. taught that treatment with β adrenergic antagonists or propranolol had no effect on protein kinetics. In contrast, the claimed invention discloses that muscle protein net balance improved 82% relative to pre-treated baseline in subjects
5 treated with propranolol while it decreased 27% in the non-treated control subjects ($p < 0.05$). Consequently, in view of the prior art of Herndon et al., applicant submits that the claimed methods with the unexpected results are patentable.

10 The Examiner also contended in the Advisory Action that the feature of improving muscle protein metabolism is not considered in determining the patentability of claims 1-7 and 9-12 because a method of treating a burn patient and a method of improving muscle protein metabolism (catabolism) are two separate inventions in view
15 of the restriction requirement imposed by the Examiner. Applicant respectfully disagrees.

Applicant further wants to point out that this rejection was not raised in the Office Action or Final Office Action. This
20 rejection was raised for the first time in the Advisory Action. Hence, the Examiner was rejecting the claims based on a rejection against

which Applicant did not have any chance to respond to before the Final Office Action.

The non-elected claims are drawn to a method of using a
5 beta-adrenergic antagonist to decrease protein catabolism and
increase lean body mass in an individual. In contrast, claims 1-7 and
9-12 are drawn to methods of treating an individual having a severe
burn with beta-adrenergic antagonist or propranolol because the
treatment would improve skeletal muscle protein kinetics in the
10 treated individual. Claims 1-7 and 9-12 are not drawn to nor recite
limitation recited in the non-elected claims. Hence, Applicant submits
that claims 1-7 and 9-12 do not fall in the realm of the subject matter
of the non-elected claims.

15 In conclusion, a claim is anticipated only if each and every
element as set forth in the claim is found, either expressly or
inherently described, in a single prior art reference. The identical
invention must be shown in as complete detail as is contained in the
claim. In view of the fact that Herndon et al. clearly taught that
20 treatment with β adrenergic antagonists or propranolol had no effect
on protein kinetics in burn patients, whereas the present invention
discloses treatment with beta-adrenergic antagonist or propranolol

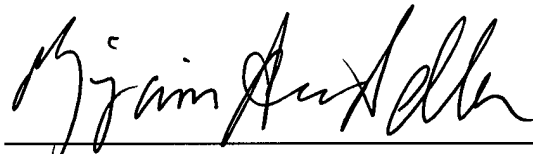
would improve skeletal muscle protein kinetics in burn patients, the present invention is not anticipated by Herndon et al. Consequently, Applicant respectfully requests that the rejection of claims 1-7 and 9-12 under 35 U.S.C §102(b) be withdrawn.

5

Respectfully submitted,

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Date: Jan 15, 2003



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CLAIMS ON APPEAL

1. (twice amended) A method of treating an individual having a severe burn, comprising the step of administering to said individual a pharmacologically effective dose of a beta-adrenergic antagonist, wherein treatment with said beta-adrenergic antagonist improves skeletal muscle protein kinetics in said individual as compared to individual without said treatment.

2. The method of claim 1, wherein said beta-adrenergic antagonist is administered intravenously.

3. The method of claim 2, wherein said beta-adrenergic antagonist is administered in a dose that decrease heart rate in said individual by about 25%.

4. The method of claim 2, wherein said beta-adrenergic antagonist is administered in a dose of from about 0.1 mg/kg of the body weight of the individual to about 10 mg/kg of the body weight of the individual.

5. The method of claim 1, wherein said beta-adrenergic antagonist is selected from the group consisting of propranolol, timolol, nadolol, atenolol, metoprolol, esmolol, nipradilol, carvedilol and acebutolol.

5

6. The method of claim 1, wherein said beta-adrenergic antagonist is propranolol.

7. (amended) The method of claim 6, wherein said
10 propranolol is administered intravenously in a dose of about 1
mg/kg of the body.

9. (twice amended) A method of treating an individual
having a severe burn, comprising the step of administering to said
15 individual a pharmacologically effective dose of propranolol, wherein
treatment with said propranolol improves skeletal muscle protein
kinetics in said individual as compared to individual without said
treatment.

20 10. The method of claim 9, wherein said propranolol is
administered intravenously.

11. The method of claim 9, wherein said propranolol is administered in a dose that decrease heart rate in said individual by about 25%.

5

12. The method of claim 9, wherein said propranolol is administered in a dose of from about 0.1 mg/kg of the body weight of the individual to about 10 mg/kg of the body weight of the individual.